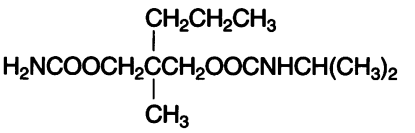
Carisoprodol

CAS #78-44-4
Swiss CD-1 mice, at 0.0, 300.0, 750.0, and 1200 mg/kg by gavage
Jerrold Heindel, NTP/NIEHS Project Officer,
Julia George, Patricia Fail, and Tom Grizzle, Research Triangle Institute
Started 5/31/88; Completed 10/1/91
NTIS #PB92128404



Carisoprodol, used as a centrally acting muscle relaxant and analgesic, crosses the placenta and is concentrated in breast milk. Because other carbamates have produced reproductive toxicity, CAR was tested for its effects on reproduction and fertility in Swiss CD-1 mice, following the RACB protocol (Grizzle et al., Fundam Appl Toxicol 24:132–139 [1995]). Data on body weights, food and water consumption, and clinical signs were gathered in the Task 1 dose-range-finding study and used to set exposure concentrations for Task 2 of 300, 750, and 1200 mg/kg by gavage. Feed and water consumption were increased only at the top dose by 10 to 20%. The top dose induced considerable lethargy for the first 3 to 4 weeks of dosing, after which the incidence and severity of this effect abated.

During Task 2, dam weight at delivery in the high dose females was reduced at the fourth and fifth litters (by 6 and 7%, respectively). Sire weights were not affected during Task 2. While there was no treatment-related change in the mean number of litters per pair, the number of live pups per litter, or viability, there was a 7% reduction in pup weight adjusted for litter size.

A crossover mating trial was performed using the control and high dose mice. There were no differences between any of the groups: the number and weight of pups were unchanged, as were the mating and fertility indices.

After the Task 3 pups were delivered and evaluated, the control and high dose F_0 mice were killed and necropsied. There was no treatment-related effect on male body weights or organ weights, with the exception of increased weights for liver (23%) and epididymis (11%). There were no changes induced in any sperm measure. For females, there was a 16% reduction in the body weight of the treated mice; no other differences were observed. No treatment-related microscopic lesions were observed in the liver, kidney, adrenals, or reproductive organs.

The last litter in Task 2 from all dose groups was reared by their dams until weaning, when they began receiving the same dose of CAR administered to their parents. During the nursing period, there was increased mortality of female pups in the middle dose group only, to a maximum of 13% loss of pups. Body weight at weaning was reduced by 11% (all treated females) and 12% (high dose males).

When the F_1 mice at all dose levels were mated within dose groups at approximately 74 days of age, there was, at the high dose, a 22% reduction in the number of live pups per litter, and a 7% reduction in adjusted live pup weight. Postpartum F_1 dam weights were reduced in the low and high doses by 6 and 7%, respectively. Feed and water consumption by the F_1 adults was increased by 12 to 20% in the middle and high dose groups, respectively.

After delivery of the F_2 pups and a short recovery period, the females were subject to vaginal lavage for 12 days, and then the adult F_1 mice from all dose levels were killed and necropsied. Male body weights were reduced in the middle and high dose groups by 6 and 9%, respectively. Adjusted liver weights in those same groups of males were increased by 10 and 20%, respectively. Right testis weight was reduced by 12% at the high dose level. There was no difference in any sperm measure. Female body weights were reduced by 5, 6, and 8% (low to high dose levels), while relative liver weights were increased by 8, 13, and 18%, respectively. There were no observed changes in estrous cyclicity end points. There were no treatment-related microscopic lesions noted in the livers, kidneys, adrenals, or reproductive organs. Incidental macroscopic lesions were noted, scattered among the dose groups, and not considered treatment related.

In summary, carisoprodol produced reproductive toxicity in the second generation (reduced F_2 pup number and weight) at exposure levels that produced significant behavioral effects initially and alterations in somatic and organ weights.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **92128404**
Chemical: **Carisoprodol**
CAS#: **78-44-4**
Mode of exposure: **Gavage**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	300 mg/kg	750 mg/kg	1200 mg/kg
General toxicity	Male, female	Male, female	Male, female
Body weight	—, —	—, —	—, ↓
Kidney weight[a]	•	•	—, —
Liver weight[a]	•	•	↑, —
Mortality	—, —	—, —	↑, ↑
Feed consumption	•	•	—, •
Water consumption	•	•	—, •
Clinical signs	—	—	—
Reproductive toxicity			
x̄ litters/pair	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	—, ↓
Cumulative days to litter	—	—	—
Absolute testis, epididymis weight[a]	•	•	—, ↑
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	—, —, —
Estrous cycle length	•	•	—

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	—	—

F_1 generation — Dose concentration →	300 mg/kg	750 mg/kg	1200 mg/kg
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, ↓	—, ↓	↓, ↓
Mortality	—, —	—, ↑	—, —
Adult body weight	—, ↓	↓, ↓	↓, ↓
Kidney weight[a]	—, —	—, —	—, —
Liver weight[a]	—, ↑	↑, ↑	↑, ↑
Feed consumption	—, —	↑, —	↑, ↑
Water consumption	—, —	↑, —	↑, —
Clinical signs	—	—	—
Reproductive toxicity			
Fertility index	—	—	—
# live pups/litter; pup wt./litter	—, —	—, —	↓, ↓
Absolute testis, epididymis weight[a]	—, —	—, —	↓, —
Sex accessory gland weight[a] (prostate, seminal vesicle)	—, —	—, —	—, —
Epidid. sperm parameters (#, motility, morphology)	—, —, —	—, —, —	—, —, —
Estrous cycle length	—	—	—

Summary information	
Affected sex?	Unclear
Study confounders:	None
NOAEL reproductive toxicity:	750 mg/kg
NOAEL general toxicity:	<300 mg/kg
F_1 more sensitive than F_0?	Yes
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.